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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,745	CASIMIR, COLIN MAURICE	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/202008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-67* is/are pending in the application.

4a) Of the above claim(s) *49 and 57-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-48 and 50-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/09/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 05/20/2008 has been entered. Claims 1-42 are cancelled. Claim 43 is amended. Claims 43-67 are pending.

Claims 49 and 57-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 43-48 and 50-56 are currently under examination.

This application 10/520,745 filed on Aug. 22, 2005 is a 371 of PCT/GB03/03012 filed on 07/11/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claims 43-48 and 50-56 **remain** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's arguments filed on 05/20/2008 have been fully considered and found not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 3-4 of the office action mailed on 11/19/2007.

Claim 43 has been amended and no longer recites "wherein said viral particle is enveloped using an envelope unable to naturally bind to cells of a species being targeted, *said*

viral particle in a first cell binding activity wherein the viral packaging cell also contains nucleic acid encoding a passenger peptide binding moiety" in step (i). This aspect of the rejection is *withdrawn*.

The amended claim 43 continues to recite the two contradicting limitations in step (ii): limitation "expressing the viral nucleic acid and nucleic acid encoding the passenger peptide binding moiety and incorporating said passenger peptide binding moiety into said packaging cell membrane ---" and limitation "wherein the passenger peptide binding moiety is other than a chimeric or fusion protein and wherein said passenger peptide is other than one derived from the virus or said packaging cell". This aspect of the rejection is *maintained* of the record.

Applicant argues that the current invention demonstrates that a naturally occurring cellular surface protein, not normally present on the surface of the retroviral packaging cells can be incorporated into the surface of retroviral particles. Applicant argues that the "passenger peptide" would normally be a protein not expressed by the fibroblast (HEL293 most commonly) used to package the retrovirus, and this is incorporated into the cell by transfection using calcium phosphate or lipids (standard technology known in the art). Applicant indicates that the inventor has made use of plasmid vectors that allow easy establishment of stable transfectants (for lentiviral work transient transfection is used) (See page 11 of Applicant's reply filed on 05/20/2008).

In response, the Examiner notes that claim 43 as written reads on various possibilities that the nucleic acid encoding the passenger peptide binding moiety is being engineered either as part of the genome of recited packaging cell or as an extrachromosomal nucleic acid, or as part of the genome of the recited viral particle. In this regard, amended claim 43 as written can be

considered as broad, but not indefinite, and the issues will be further discussed in the enablement rejection. However, regardless where the "passenger peptide" is expressed from, it remains unclear why the passenger peptide binding moiety incorporated into said packaging cell membrane is not considered as being derived from the said packaging cell. Based on Applicant's arguments, a plasmid vector expressing the "passenger peptide" renders the "passenger peptide" incorporated in the cell membrane of the recited packaging cell, and upon budding of the co-expressing viral particle, the "passenger peptide" becomes incorporated in the viral particle. As the "passenger peptide" is incorporated as part of cell membrane of the packaging cell line, the "passenger peptide" is derived from the said packaging cell. Therefore, the Examiner maintains the position that it is unclear how the recited passenger peptide-binding moiety is incorporated into the packaging cell membrane, and at the same time, the passenger peptide is not considered as derived from the packaging cell.

Claim Rejection – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 43-48 and 50-56 **remain** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a retroviral particle having a modified cell binding activity, comprising the steps of providing a retroviral packaging cell, wherein the retroviral packaging cell contains viral nucleic acid encoding an enveloped viral particle that is unable to naturally bind to a target cell; and transfecting said retroviral packaging

cell line with an expression vector comprising a heterologous nucleic acid sequences encoding membrane bound human stem cell factor (mbSCF) operably linked to an eukaryotic promoter such that human mbSCF is expressed on the membrane of the packaging cell wherein a resulting retroviral particle produced from said packaging cell bears human mbSCF on the envelope of the retroviral particle that directs the binding of the retroviral particle to a target cell expressing c-kit on the membrane of said target cell, **does not** reasonably provide enablement the said method for **(i)** a nucleic acid encoding any peptide binding moiety other than human stem cell factor (SCF), or **(ii)** any target cell other than the target cell expressing c-kit receptor on its cell membrane, or **(iii)** a method comprising steps of making a retroviral particle having a modified cell binding activity, wherein the modified cell binding activity of said retroviral particle is determined by any non-Envelope-receptor interactions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Previous rejection is ***maintained*** for the reasons of record advanced on pages 5-12 of the office action mailed on 11/19/2007.

The issues contributing to the lack of predictability revealed in the prior arts and identified in the previous Non-Final rejection mailed on 11/195/2007 include (a) the size limitation and resulting intracellular location of any given passenger peptide binding moiety (including a non-cell membrane bound peptide) other than human SCF that can be expressed from the packaging cell such that the passenger peptide binding moiety is incorporated into the envelope of a given retroviral particle, (b) cross interaction between a passenger peptide binding moiety and a receptor affecting recited altered tropism of a viral particle, a process involving the

topology and expressed levels of the introduced passenger peptide binding moiety in the viral envelope and the topology and expressed levels of its corresponding receptor(s) present on the cell surface under a given growth condition, (c) viral tropism determined by contacts between viruses and cell occur outside of the *bona fide* Env-receptor interaction, and (d) potential immune and inflammation responses as a result of introduced passenger peptide binding moiety and cell-derived components being concentrated along with viral vector particle.

Issues of unpredictability related to (a) and (b) are relevant to why specific interaction between the passenger peptide incorporated into the viral envelope and the receptor on the target cell is required to overcome the breadth of the claims relevant to **(i)** and **(ii)** (see enabled scope set forth above). The issue (c) is directly relevant to why *bona fide* Env-receptor interaction contributing to the viral tropism renders the claimed method as listed in the rejection of said method **(iii)** considered not enabled for the methods. In this regard, as discussed on page 11 of Non-Final office action mailed on 09/05/2006, how a virus infects its host cell is determined by many factors including, but not limited to, the interactions between viral envelope proteins and receptor/co-receptor proteins on cell surface. Manel et al. reviewed the HTLV-1 tropism and envelope receptor stated, "--- tropism depends on many parameters that are independent of Env-receptor interactions, ---"(page 6022, right column, third paragraph under Conclusions and perspectives, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene.* 24(39): 6016-25, 2005). For instance, "contacts between viruses and cell also occur outside of the *bona fide* Env-receptor interactions that lead to productive viral replication" (page 6016, right column, second paragraph, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene.* 2005 24(39): 6016-

25, 2005). Issue (d) is relevant to the rejection of said method in the non-enabled embodiments (i), (ii), and (iii).

Applicant's Arguments

Applicant states that the main thrust of the rejection relates to the Examiner's position that the incorporation of a passenger peptide into the viral particle using the methods of the current invention is inherently unpredictable, with the exception of the working example in the specification (mbSCF), the method is not considered to be easily transferable for use with other peptides.

With regard to incorporation of membrane proteins into viral particle, Applicant argues that good evidence exists that the majority of proteins present on the cell surface become incorporated into retroviral particles. For example, see Hammarstedt et al. (2000) Minimal exclusion of plasma membrane proteins during retroviral envelope formation. PNAS USA. 97:7527-7532, also, Arthur et al (1992, Cellular proteins bound to immunodeficiency viruses: implications for pathogenesis and vaccines. Science 258: 1935- 1938). Applicant indicates that these publications are attached as Exhibit A and Exhibit B, respectively. Applicant argues that these references have shown that retroviruses made in cells from different strains of mice are immunologically distinct and have surface proteins characteristic of the specific host cell. Therefore, Applicant argues that the incorporation of membrane associated peptides into budding viruses is eminently predictable (See page 13 of Applicant's reply filed on 05/20/2008).

With regard to the properties of membrane proteins to be incorporated into viral particle, Applicant states that the Examiner has cited particular properties of the membrane proteins that would allegedly affect the predictability of the transferability of the methods to other proteins.

Applicant argues that these objections are all believed to have been addressed by the teaching of Hammarstedt et al (2000), which shows that virtually all plasma membrane proteins from the host cell are present in the retroviral particle. Applicant argues that the only requirement for retroviral incorporation appears to be that the protein resides in membrane structures known as "lipid rafts" (Esser et al. (2001) Differential incorporation of CD45, CD80 (7--1), CDS6 (B7-2), and major histocompatibility complex class I and II molecules into human immunodeficiency virus type I virions and microvesicles: implications for viral pathogenesis and immune regulation. J Virol. 75; 6173-6182) (attached as Exhibit C). Applicant argues that there are no limits to the size of the protein that may be incorporated; the protein must simply reside in the cell membrane, and such proteins may be easily identified by the skilled person. Applicant further argues that other properties of the passenger peptide, such as charge, folding, post-translational modification, hydrophobicity, etc. would also have no relevance in terms of its incorporation into the viral particle membrane. Applicant states that the passenger peptide is expressed by the packaging cells and incorporated into the plasma membrane independent of the viral particle genome, and the passenger peptide is then incorporated into the budding viral particle in a highly predictable manner irrespective of its properties (See pages 15-16 of Applicant's reply filed on 05/20/2008).

With regard to the binding properties of membrane proteins, Applicant argues that as demonstrated in Applicant's mbSCF example, and previously indicated interactions between the passenger peptide binding moiety and other receptors or unintended proteins do not affect the claimed altered tropism. Applicant argues that, the claimed method does not modify the properties of the passenger peptide therefore its specific binding properties will be maintained.

Applicant argues that if the surface proteins of viral particles are not modified there is no reason for them to lose their binding properties. Applicant argues that interactions between the viral particles and target cells (or otherwise) that are independent of the specific passenger peptide/cognate receptor interactions does not affect the viral particle tropism because. The infectious titer of ecotropic virus on human cells is phenomenally low, which is generally below the limits of detection of most assays (See pages 16-17 of Applicant's reply filed on 05/20/2008).

With regard to immune and inflammatory responses, Applicant argues that unwanted immune and inflammatory responses to the viral particles and passenger peptide does not contribute to the alleged lack of predictability because Applicant has shown in previous remarks that many studies have been carried out using viruses of the virus families postulated and that these have not shown adverse immune responses to the viral particles and the passenger peptide would be selected by the skilled artisan specifically to minimize potential adverse immune responses. Any foreign protein has the potential to illicit an immune response, but any potential immunogenicity of the viral particles is believed not to be relevant to enablement or written description issues or relevant to the patentability of the current invention. Applicant indicates that previously cited Cronin et al (2005) has again been cited as evidence that cell-derived components are concentrated on the surface of viral particles leading to potential immune responses. In this regard, Applicant argues that the potential targeting peptides by their nature would be cellular products and should have low immunogenicity, and indeed, any potential immunogenicity may well be exploited for the production of vaccines and is therefore not necessarily undesirable. Applicant states that the Examiner also has raised another immune response concern having to do with the nature of the passenger peptide's association with the

viral particle (it is attached to the membrane rather than covalently linked to the viral envelope protein). In this regard, Applicant argues that the passenger peptide is necessarily a membrane associate protein (or else the invention would not work), therefore, such proteins do not simply "fall" out of membranes, and indeed, their hydrophobic nature would make them insoluble and exceedingly unlikely to dissociate from the membrane even in the event of the destruction of the viral particle.

Applicant argues that the viral envelope is not modified, and the two references cited by the Examiner, Gritsun et al. and Hayasaka et al. relate to flaviviruses and it is clear that flaviviruses are of little relevance to the current invention because Flaviviruses cannot be used as long term gene transfer vehicles because they are RNA viruses. Applicant argues that these references are concerned with variability in the envelope proteins of these viruses affecting their properties, but the current specification does not discuss envelopes (as the inventors do not modify them) other than to specify that the envelope used needs to be incapable of binding to the target cells. Applicant argues that it would be clear to the skilled person that micro heterogeneity in the envelopes of these viruses is not relevant.

Applicant argues that further evidence to support applicant's position that the current invention is transferable to other membrane proteins and targets may be found in Yang et al (2006) Targeting lentiviral vectors to specific cell types in vivo. PNAS USA 103(31): 11479--11484 (attached as Exhibit E). Applicant indicates that the authors show that a strategy similar to that used in the current invention may be used to target lentivirus particles to B cells using antiCD20 incorporated on the surface of the viral particle.

Response to Applicant's Arguments

Applicant's arguments filed 05/20/2008 have been fully considered but they are not persuasive because of the reasons discussed below.

First of all, it is worth noting that the breadth of claimed invention encompasses *in vitro* and *in vivo* methods of making any viral particle having any modified cell binding activity via incorporation of any "passenger peptide" that has been incorporated into cell membrane of any packaging cell line. Therefore, Applicant's arguments that the two references cited by the Examiner, Gritsun and Hayasaka, relate to Flaviviruses and that Flaviviruses are of little relevance to the current invention since Flaviviruses cannot be used as long term gene transfer vehicles as they are RNA viruses, are not persuasive because the claimed invention reads on any virus.

In response to the arguments pertaining to incorporation of membrane proteins into viral particle, the Examiner notes Hammarstedt et al. (2000) and Arthur et al (1992) do report the association of plasma membrane proteins with retroviral particles such as HIV during retroviral envelope formation. However, the Examiner notes that Hammarstedt et al. (2000) and Arthur et al (1992) do not teach the retroviral particles with associated plasma membrane proteins derived from packaging cell line exhibit "modified cell binding activity" as claimed in instant application. Therefore, the report by Hammarstedt et al. (2000) and Arthur et al (1992) on association of plasma membrane proteins with retroviral particles fail to support the claimed "modified cell binding activity" of the retroviral particle.

In response to the arguments pertaining to the properties of membrane proteins to be incorporated into viral particle, the Examiner notes that, as discussed in the preceding paragraph,

that the teaching of Hammarstedt et al (2000) merely shows that plasma membrane proteins from the host cell are present in the retroviral particle. Hammarstedt et al (2000) does not support the plasma membrane proteins associated with the retroviral particles exhibit "modified cell binding activity". To the contrary of the claimed "modified cell binding activity" of the retroviral particle encompassed by the claimed method, the fact that the retroviral particles with associated plasma membrane can continue to infect and prorogate in the packaging cells after budding out from a given packaging cell argues against the notion the "cell binding activity" (i.e. tropism of the virus) of the retroviral particles have been modified as the result of plasma membrane association. It is worth noting again that the claimed invention encompasses any "passenger peptide" associated with (or incorporated in) any given viral particle will result in "modified cell binding activity" of the viral particle, which is simply not the case as reported by Hammarstedt et al. (2000) and Arthur et al (1992).

In response to the arguments pertaining to the binding properties of membrane proteins and potential modification of viral envelope by association with claimed "passenger peptide", it is worth noting that for a given membrane protein to be functional, it requires proper expression, modification, protein folding, incorporation into a given membrane environments etc. To demonstrate the foundation of this aspect of the rejection, **Parmley et al.**, 2007, teaches that even silent SNPs (single nucleotide polymorphisms) encoding the same amino acid residues are not necessarily neutral with regard to their effects on the functions of polypeptides, and there are two additional mechanisms affecting the function of a given polypeptide: (1) modification of protein structure and activity, mediated by induction of translational pausing during co-translational protein folding, and (2) modification of protein abundance mediated by alteration in

mRNA stability via changed secondary structures of mRNA, which in turn leads to perturbation in protein synthesis (See abstract, Parmley et al., How do synonymous mutations affect fitness? *Bioessays*, 29(6): 515-9, 2007). In other words, alterations in either protein folding or translational efficiency result on changed protein functions encoded by synonymous mutations. This has been clearly demonstrated in the membrane bound P-glycoprotein, which **Kimch-Sarfaty et al.** reports that a "silent" polymorphism in the MDR1 gene change substrate specificity of the encoded P-glycoprotein (See Kimch-Sarfaty et al. A "silent" polymorphism in the MDR1 gene changes substrate specificity. *Science*, 315(5811):525-8, 2007). Therefore, Applicant arguments that properties of the passenger peptide, such as charge, folding, post-translational modification, hydrophobicity, etc. would have no relevance in terms of its incorporation into the viral particle membrane, are not persuasive because binding properties of a given membrane protein exemplifies the function of the membrane protein (i.e. the claimed "passenger peptide"). Pertinent to the same aspect of the rejection, Applicant arguments that the claimed method does not modify the properties of the passenger peptide therefore its specific binding properties will be maintained have been fully considered and found not persuasive. This is because that in order to exhibit "modified cell binding activity", the receptor/cognate binding function of claimed "passenger peptide" has to be dominant over the claimed "first binding activity" displayed by the endogenous viral envelope proteins. In other words, the endogenous viral envelope proteins are modified, at least at overall topological geometry of viral envelope, by the association of "passenger peptide" to the extent that the associated "passenger peptide" becomes the main determinant of viral tropism. In this regard, as discussed earlier in this office action, the reports by Hammarstedt et al. (2000) and Arthur et al (1992) on association of plasma

membrane proteins with retroviral particles fail to support the claimed "modified cell binding activity" of the retroviral particle.

In response to the arguments pertaining to immune and inflammatory responses that the potential targeting peptides by their nature would be cellular products and should have low immunogenicity, and indeed, any potential immunogenicity may well be exploited for the production of vaccines and is therefore not necessarily undesirable, have been fully considered and found not persuasive, the Examiner notes that it has been documented in the previous office action that "Cronin et al. stated, one problem with the methods outlined is that cell-derived components are concentrated along with the vector particles leading to potential immune and inflammation responses (See page 390, second paragraph, Cronin et al., Altering the tropism of lentiviral vectors through pseudotyping. Curr Gene Ther. 5(4): 387-98, 2005; this reference has been cited in the Non-Final office action mailed on 09/05/2006)". Again, the Examiner notes that breadth of claimed invention encompasses both *in vitro* and *in vivo* methods of making any viral particle having any modified cell binding activity via incorporation of any "passenger peptide" that has been incorporated into cell membrane of any packaging cell line. Considering the claimed method of expressing an antigenic foreign membrane protein isolated from a given species of organism, which is the claimed "passenger peptide", to be incorporated into a given plasma membrane of a given host mammalian cell of distinct species *in vivo*, it is unpredictable whether targeted co-expression of a viral particle to be modified in cell binding activity and the "passenger peptide" can be achieved. Issues pertaining to the unpredictability of targeted gene expression via various administration routes have been well documented in the literature of gene therapy, which is encompassed by the *in vivo* aspect of claimed method. With regard to targeted

gene expression in the context of claimed *in vivo* method of instant application, even if targeted co-expression of "passenger peptide" and a viral particle to be modified can be achieved *in vivo* (e.g. a mouse), it remains unpredictable whether the antigenic foreign "passenger peptide" can survive the attack by immune system before the viral particle of interest can infect the cells expressing this foreign "passenger peptide". This level of experimentation is considered as undue because every membrane protein (i.e. a "passenger peptide" to be expressed) has its characteristics and functions, targeted expression of a given membrane protein to a given cell in vivo requires case-by-case investigation. To demonstrate the foundation of this aspect of rejection, for instance, **Proesmans et al.** teaches that since the discovery of the CFTR gene in 1989, CF has been considered a prime candidate for gene therapy by targeted gene expression to cell having defective CFTR gene. However, Proesmans et al. states that the delivery of the normal gene to CF lungs involves several challenges, including the identification of an acceptable vector; moreover, reaching the epithelial cells can be hazardous because of the thick mucus. Additionally, Proesmans et al. states that host-specific immune responses generated against a virus-derived vector or even the therapeutic CFTR protein may pose a problem (See bridging paragraph, page 845, Proesmans et al., What's new in cystic fibrosis? From treating symptoms to correction of the basic defect, *Eur J Pediatr.* 167(8):839-49, 2008). It is worth noting that, considering a "passenger peptide" expressed from a transfected vector as Applicant indicates for the claimed methods, Applicant's arguments that there are no limits to the size of the protein that may be incorporated, and the protein must simply reside in the cell membrane, are found not persuasive because, for instance, proper expression of functional CRTR from a vector has been unpredictable as discussed by Proesmans et al.

In conclusion, the specification as filed fails to provide any specific guidance and/or working examples, regarding non-retroviral particles. The specification also fails to direct the skilled artisan to any teachings on the relationship between the control of the expression level of a passenger peptide binding moiety and its incorporation into viral particles, and how the relationship may affect the recognition between a passenger peptide and its receptor, and the infectivity the viral particles to specific target cells, which would allow one of skill in the art to make and use the claimed invention without undue experimentation. In view of the state of the unpredictability in the art, and the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to practice the breadth of the claimed invention.

Claim Rejection – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 43-46 and 54-56 remain rejected under 35 U.S.C. 102(b) as being anticipated by Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000). Applicant's arguments filed on 05/20/2008 have been fully considered and they are not persuasive. Previous

rejection is ***maintained*** for the reasons of record advanced on pages 8-9 of the previous office action mailed on 06/05/2007, and summarized below.

Soong et al. teach a method molecular breeding of viruses, including retrovirus (which reads on an enveloped viral particle recited in claim 43 of instant application), with altered tropism without involving generation of fused viral envelope protein. Specifically, Soong et al. teach *in vitro* process of DNA shuffling (molecular breeding) mimics this mechanism on a vastly parallel and accelerated scale. Multiple homologous parental sequences are recombined in parallel, leading to a diverse library of complex recombinants from which desired improvements can be selected. Different proteins and enzymes have been improved using DNA shuffling. Soong et al. performed the first application of molecular breeding to viruses. A single round of shuffling envelope sequences from six murine leukemia viruses (MLV) followed by selection yielded a clone with a completely *new tropism* for Chinese Hamster Ovary (CHOK1) cells (See abstract, Figure 3, Soong et al., 2000).

Applicant's arguments are the same as previously presented that Soong et al did not teach the incorporation into the packaging cell membrane of a peptide that is foreign to the virus itself. Therefore the claim limitation that the passenger peptide is not derived from the packaging cell or the virus should have overcome this rejection.

In response to Applicant's arguments, it is noted that, as discussed in the maintained rejection of claims 43-48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the amended limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" is in direct contradiction with the limitation

"incorporating said passenger peptide binding moiety into said packaging cell membrane" recited in step (ii) of claim 43. As a result, the metes and bounds of either one of the two limitations cannot be determined when the other limitation is also considered.

Since the metes and bounds of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" cannot be determined, the broadest and reasonable interpretation of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" reads on any peptide that is not in the context of a given endogenous protein present in a given virus or in a given packaging cell. In other words, the limitation essentially reads on any peptide becasue any given peptide can be considered as not derived from (i.e., not in the context of) a given reference viral or a given cellular protein. Under this interpretation, the limitation certainly reads on various envelope proteins encoded by the viral nucleic acid during the molecular breeding process taught by Soong et al. Moreover, the method taught by Soong et al. doesn't involve chimeric or fusion envelope proteins, and the altered tropism is a result of accelerated evolution of existing viral envelope proteins through recombination.

Thus, Soong et al. clearly anticipates claims 43-46 and 54-56 of instant application.

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 43, 48, 50 and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. *Nature* 25(4): 436-9, 2000) taken with Dropulic et al. (U.S. patent No. 6,114,141, issued Sep. 5, 2000; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006). Applicant's arguments filed on 09/24/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 10-12 of the previous office action mailed on 06/05/2007.

Applicant's arguments are the same as previously presented that Soong et al. do not describe the passenger peptide as being heterologous. Applicant also argues that Dropulic et al. do not describe the expression of such heterologous proteins so as to be incorporated into the viral particle via the envelope. Applicant further argues that the use of recombination in gene therapy vectors is not viable ("completely taboo", as phrased by Applicant) on the basis that it is not desirable to have gene therapy vectors recombining to each other.

In response to Applicant's arguments, it is noted that, again, as discussed in the maintained rejection of claims 43-48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the amended limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" appears to be in direct contradiction with the newly amended limitation "incorporating said passenger peptide binding moiety into said packaging cell membrane" recited in step (ii) of claim 43. As a result, the metes and bounds

of either one of the two limitations cannot be determined when the other limitation is also considered.

Since the metes and bounds of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" cannot be determined, the broadest and reasonable interpretation of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" reads on any peptide that is not in the context of a given endogenous protein present in a given virus or in a given packaging cell. In other words, the limitation essentially reads on any peptide becasue any given peptide can be considered as not derived from (i.e., not in the context of) a given reference viral protein or a given reference cellular protein. Under this interpretation, the limitation certainly reads on various envelope proteins encoded by the viral nucleic acid during the molecular breeding process taught by Soong et al.

Examiner's response in more details remain the same as documented on pages 15-18 of the office action mailed on 11/19/2007.

5. Claims 43, 48, 52 and 53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000) taken with Guber et al. (U.S. patent No. 569,177, issued Nov. 25, 1997; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006). Applicant's arguments filed on 09/24/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the previous office action mailed on 06/05/2007.

Applicant's arguments and Examiner's **Response to Applicant's arguments** are essentially the same as discussed in the preceding section of the rejection of claims 43, 48, 50 and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al., 2000 taken with Dropulic et al. 2000.

Accordingly, claims 43, 48, 52 and 53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al., 2000 taken with Guber et al., 1997 is ***maintained*** of the record.

Examiner's response in more details remain the same as documented on pages 18-20 of the office action mailed on 11/19/2007.

6. Claims 43 and 47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000) taken with Yajima et al. (Retroviral vector targeting human cells via c-Kit-stem cell factor interaction. *Hum Gene Ther.* 9(6): 779-87, 1998; listed as the last reference in the IDS filed on 05/04/2007). Applicant's arguments filed on 09/24/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-16 of the previous office action mailed on 06/05/2007.

Applicant's arguments regarding the deficiency of Soong et al., 2000 pertaining to the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" remain the same as previously presented has been discussed in the preceding section on the rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al., 2000. Applicant argues again that Yajima et al. do not describe enveloped

viruses containing heterologous peptides derived from packaging cells at all, but describes a chimeric protein to a non-chimera and it is therefore believed that one skilled in the art would not be led to combine these documents nor would such a combination remove an inventive step from the present claims.

Examiner's response to Applicant's arguments regarding the deficiency of Soong et al., 2000 pertaining to the newly added limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" has been addressed in the preceding section on the rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al., 2000. With regard to the arguments Yajima et al. do not describe enveloped viruses containing heterologous peptides derived from packaging cells at all, it is noted that Yajima et al. was cited for the limitation of claim 47 (which depends from claim 43) of instant application because of its teachings of engineering a recombinant retroviral vector that can target human cells expressing a c-Kit receptor via a ligand-receptor interaction. Specifically, the ligand is a stem cell factor (SCF), which interacts with c-Kit receptor.

Accordingly, claims 43 and 47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al., 2000 taken with Yajima et al., 1998 is ***maintained*** of the record

Examiner's response in more details remain the same as documented on pages 21-22 of the office action mailed on 11/19/2007.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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